Plasma Cell Dyscrasia

Introduction

The plasma cell dyscrasias are technically B-cell lymphomas—derived from plasma cells (B-cell lineage) and occurring in focal masses not in the blood (lymphoma). But we don't want you thinking of them like that. Think of the plasma cell dyscrasias as their own subject, as immunoglobulin-secreting cancerous cells. It is what they secrete that causes the symptoms of the disease, rather than the cancerous cells themselves. This lesson is mostly on multiple myeloma and the spectrum of its disease. The remainder is on lymphoplasmacytic lymphoma (aka Waldenstrom's macroglobulinemia).

Multiple Myeloma Symptoms and Pathogenesis

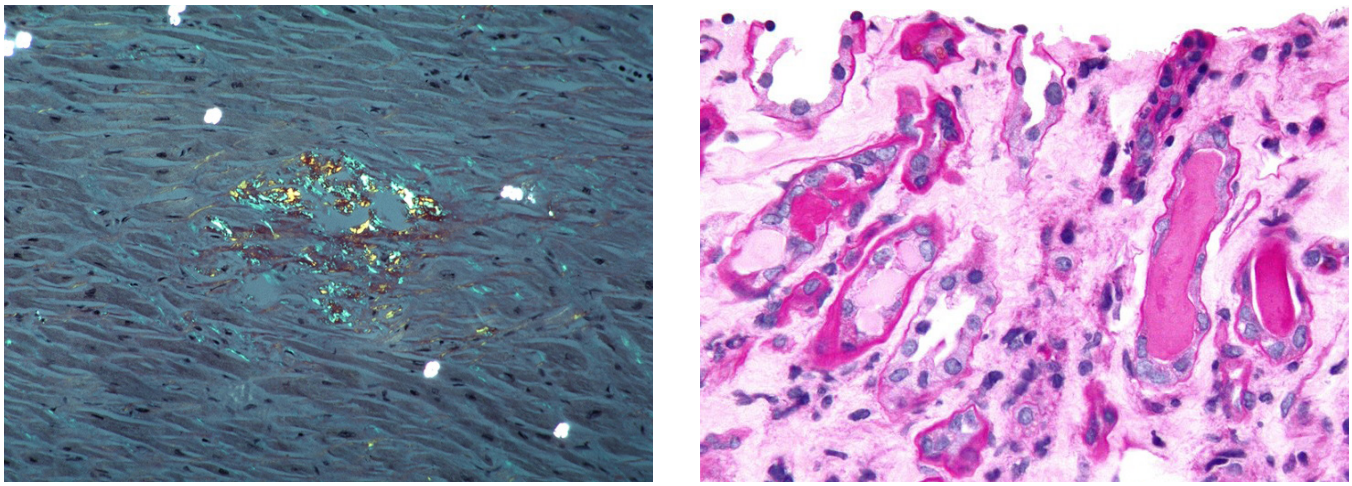
Multiple myeloma is a cancer of **plasma cells** infiltrating **bone marrow**. Bone marrow is where mature naive B cells come from; the lymph node is where they go to become mature B cells, in the way of memory B cells or plasma cells. Plasma cells aren't supposed to be in the bone marrow. Plasma cells are also supposed to last for the duration they are needed—a short burst of immunoglobulin release, secretion of antibodies to contend with an antigen, then go away when the antigen is eliminated. Plasma cells then die off and memory cells are left behind. The malignant plasma cells of multiple myeloma retain the ability to secrete immunoglobulin, though the immunoglobulin secreted is usually defective.

Myeloma arises from a malignant plasma cell that undergoes clonal proliferation—all the daughters are the same. Since this is a plasma cell, isotype switching and somatic hypermutation have already occurred. Every cancer cell has the same genes that code for exactly the same immunoglobulin. "Exactly the same" is called **monoclonal**. Monoclonal immunoglobulin identified in the blood is called an **M component**, named after the monoclonal expansion in multiple myeloma. Be careful, isotype switching has already occurred, so the immunoglobulins cannot be IgM (it is not M spike or M component because of IgM). Instead, multiple myeloma secretes **IgG** (55% of cancers), **IgA**, or **incomplete light chains**. Most cancers are a combination of immunoglobulin and light chains.

The monoclonal expansion of dysfunctional immunoglobins has several effects. First, the total protein on liver function tests is a combination of albumin and immunoglobulins. As immunoglobulins rise, there will be an **elevated protein gap.** Total protein minus albumin is the protein gap, and that number should be less than four. When the protein gap is elevated, it is indicative of excess immunoglobulins, as occurs in HIV, Hep C, and multiple myeloma. Second, because immunoglobulins are so large, they remain in plasma and can be detected on **serum electrophoresis**. Albumin is the first to be seen on the electrophoresis, and is the most abundant protein normally. In myeloma there is an **M spike** at the end of the electrophoresis. It is a spike because the immunoglobulins are identical and there are many of them. The M spike is the representation of monoclonal antibodies; an "M hump" (wider and not as tall) would be expected if antibodies came from multiple cells, polyclonal antibodies. After screening with serum electrophoresis, confirmation is made with **immunofixation**. Third, all these immunoglobulins can lead to **rouleaux formation**, stacking of red blood cells like coins. Fourth, excess dysfunctional immunoglobulins **impair normal antibody immunity**, and the patient will present with **bacterial infections**.

When **light chains** (λ more often than κ) are released, which are smaller than immunoglobulins and can exit plasma into tissue, they cause additional disease. These light chains are also known as **Bence Jones proteins**. When Bence Jones proteins get into the renal tubules, they **precipitate** in the distal nephron, where they form a cast. A cast is an accumulation of molecules in the shape of the renal tubule. This causes **myeloma kidney**, an obstructive uropathy that leads to renal failure. Those Bence Jones proteins that do not accumulate into these precipitated casts are excreted into the urine. **Urine electrophoresis** screens the urine for Ig light chains. Light chains are also **directly toxic** to tubular cells. Renal failure is one of the hallmarks of myeloma. However, light chains can deposit anywhere. "AL-type amyloidosis"

stands for **A**myloidosis **L**ight-chain. Deposition of light chains in tissue results in a deposition disease. The only thing you need to know is that AL amyloidosis **stains green on Congo red stain** and is because of myeloma.



(a) (b)

Figure 5.1: Multiple Myeloma Light Chains
(a) Congo red amyloidosis glows green. (b) Myeloma kidney shows tuybules that are obstructed by a pink proteinaceous fluid.

Hypercalcemia is another major consequence of myeloma. Hypercalcemia occurs because of **lytic lesions** caused by myeloma. Lytic lesions look like carefully punched-out areas of bone on X-ray. They are small, 1–4 cm in diameter, and visible on X-ray. A **skeletal survey** is a series of X-rays done looking for lytic lesions when the diagnosis of myeloma is being considered. Myeloma cells secrete a cytokine (MIP1-α—"mip one alpha") that stimulates **marrow stromal cells**. The stromal cells are the support for bone marrow. They normally deliver interleukin-6 to developing cells in the marrow, a growth signal. They also release **RANK-L** (the receptor activator nuclear factor κB ligand). RANK-L from stromal cells activates RANK (the receptor) on **osteoclasts**. RANK activation leads to the intracellular pathway activation involving NF-κB (nuclear factor kappa B). NF-κB stimulates osteoclasts to **clear bone**. "Clearing bone" means resorption, breaking down bone into calcium and phosphate. Myeloma cells also secrete chemokines that **inhibit osteoblasts** (osteoblasts build bone). The excess release of calcium into the blood results in hyper (elevated) calc (calcium) emia (in the blood). But because the osteoclasts and osteoblasts are activated only in the immediate region of the cancerous plasma cells, the bone resorption, and therefore local bone density, is decreased in only a small region of bone. The remaining bone is normal, giving the punched-out or lytic appearance. Do not be fooled—while these appear to be punched out on X-ray (because the cortical bone density is compromised), there is something there—cancer. If you excise one, it will be flush with red, fleshy color, a product of the tumor.

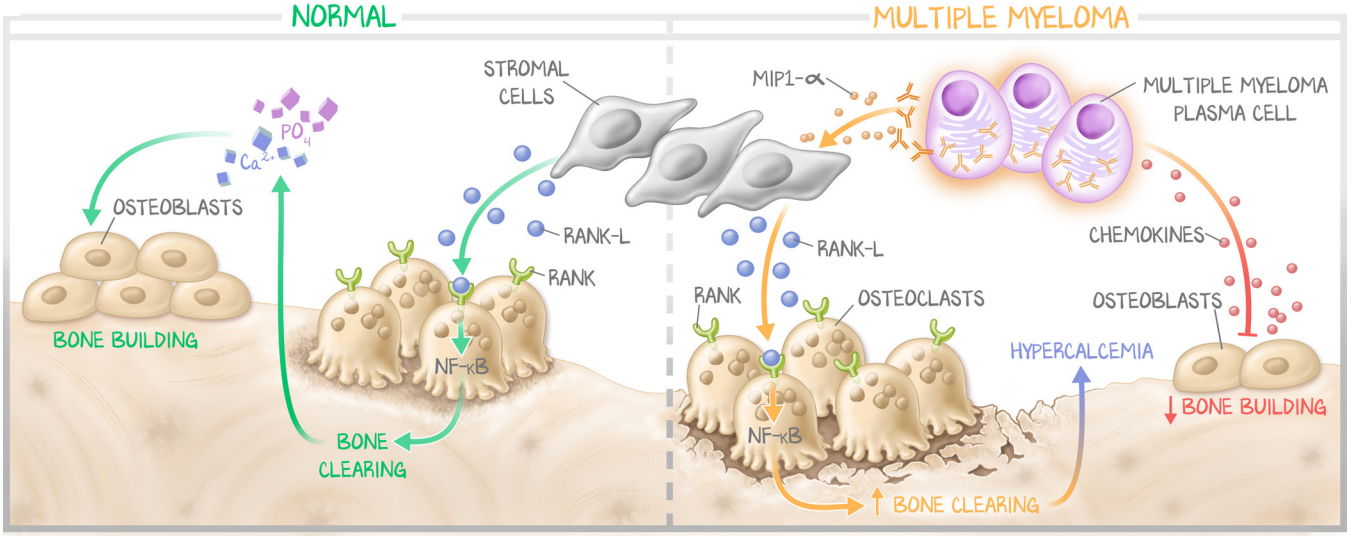
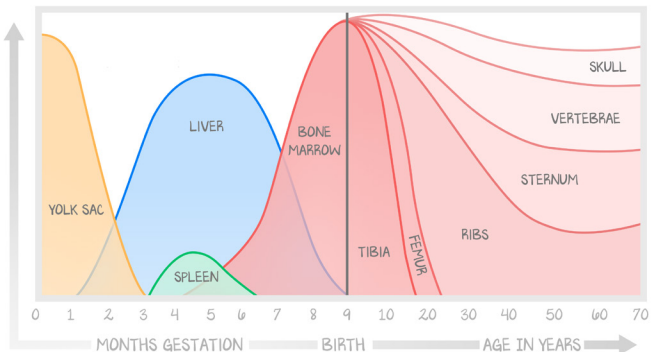
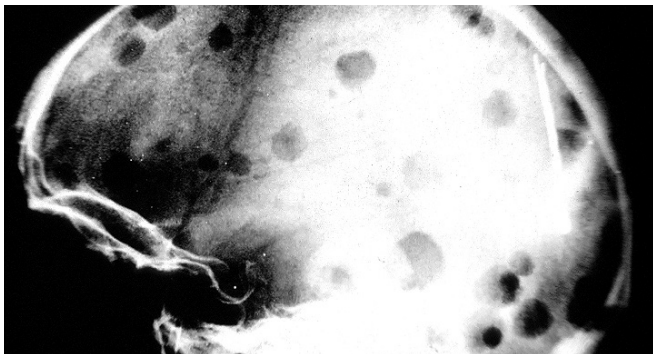


Figure 5.2: Osteoclasts, Osteoblasts, and Myeloma
Don't be confused by the name or the nomenclature. RANK-L from stromal cells, RANK on osteoclasts, cytoplasmic NF-κB activates osteoclasts by acting as a signal transducer. An unknown mechanism inhibits osteoblasts. IL-6 is released from stromal cells and from myeloma cells that induce a growth signal.

The plasma cells are in red marrow, hematopoietic marrow. They communicate to the stromal cells of the bone to then cause resorption of the cortical bone, resulting in lytic lesions and hypercalcemia. Therefore, the bones that are most likely to be affected are those that are the bones of hematopoiesis. Because multiple myeloma is a **disease of the elderly** (almost all cases are in people aged greater than 60 years) the sites of normal hematopoiesis are limited. The **skull**, **vertebrae**, and to a lesser extent the **ribs** are the most affected. Lytic lesions will therefore be in those tissues. These lesions can hurt. **Bone pain** is another major symptom of myeloma. Worse, **pathologic fractures** can occur in affected bone. Because bone resorption has compromised bone density, just walking down a flight of stairs may fracture a vertebra. Fractures hurt more than the myeloma lesions do.



(a)



(b)

Figure 5.3: Multiple Myeloma Lytic Lesions
(a) While "the marrow" is the source of hematopoiesis throughout life outside of the womb, certain bones are more likely to continue to express red marrow in old age. (b) Lytic lesions appear punched out.

The plasma cells are in the red marrow, the marrow of hematopoiesis. As they begin to increase in number, they begin to crowd out that marrow. This further weakens immunity, but more importantly leads to **anemia**.

What we've been doing in this section is explaining the key features of the diseases and their pathogeneses. The mnemonic **Old CRAB** is the organizer for multiple myeloma, used to remind you that it happens to old people (age > 60), and causes **calcemia** (hypercalcemia from bone resorption), **renal failure** (light chains precipitating in distal nephron), **anemia** (crowding out the marrow), and **bone pain** (from pathologic fractures from weakened bone).

Multiple myeloma is a molecularly and genetically homogeneous disease—there is no one mutation or translocation that results in the disease. In the very final stages of disease, resulting in plasma cell leukemia (plasma cells in the blood) there will have been an accumulation of the B-cell translocations—t(14;18), t(11;14), and t(8;14)—but they are responsible for dedifferentiation and spread and not the pathogenesis or symptoms of multiple myeloma.

The proliferation and survival of myeloma cells are dependent on several cytokines, most notably **interleukin-6**. IL-6 is an important growth factor for plasma cells. Tumor cells provide themselves with an **autocrine IL-6 signal**, as well as trick the stromal cells to feed them more IL-6. High serum levels of IL-6 are seen in patients with active disease, and are associated with a poor prognosis.

Multiple Myeloma Diagnosis and Management

When a patient is first suspected of having multiple myeloma, screening tests are performed. They have already been mentioned—the serum protein electrophoresis (SPEP) looking for the M spike, the urine protein electrophoresis (UPEP) looking for Bence Jones proteins, and a skeletal survey looking for lytic lesions. To **confirm** the diagnosis, a **bone marrow biopsy** must show **greater than 10% blasts**.

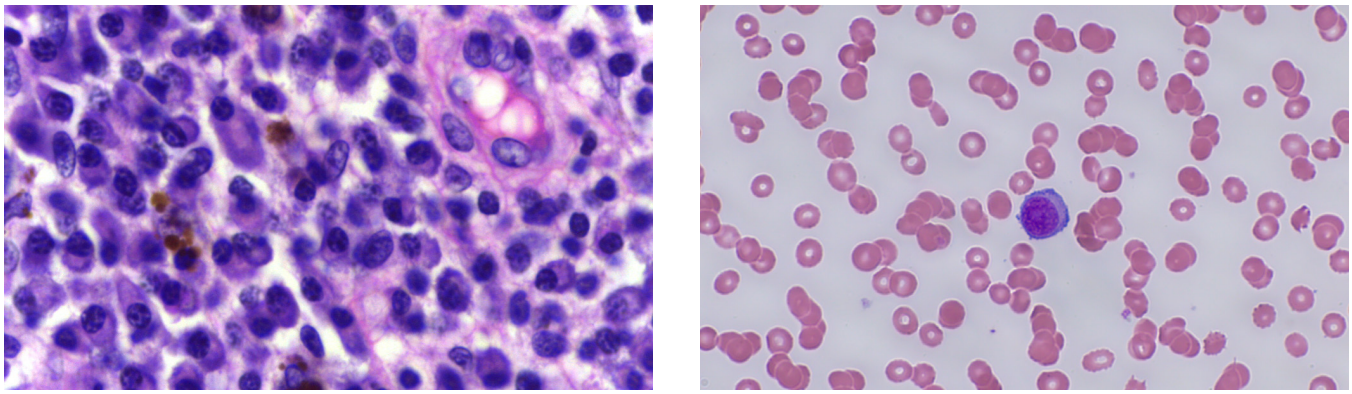
The treatment for multiple myeloma depends on the patient's age. If the age is < 65, **chemotherapy** and an **autologous stem cell transplant** are performed. These details you don't have to know, but it is interesting enough for us to include. The patient is given induction chemo, baby chemo, to deplete the marrow of obviously dividing cancer cells. This makes the harvested marrow less likely to have cancer cells. We take good marrow from the patient, and store it. We then bomb the patient's marrow with megatoxic doses of melphalan. The entire marrow is destroyed, healthy cells and myeloma cells both, obliterated. The good marrow harvested from the person is then put back into the patient. For those in whom ASCT is not an option, alternative chemotherapy regimens are available. Those, you definitely do not have to know.

Myeloma Spectrum

Monoclonal gammopathy of uncertain significance (**MGUS**) is what you say of someone who **has an M spike** but nothing else. The UPEP is negative, the skeletal survey is negative, and the bone marrow biopsy (if one is done) has < 10% plasma cells. MGUS got its name because when we discovered it, science wasn't sure whether it represented early myeloma or not. We used to teach that MGUS did not progress to multiple myeloma, and that they were not a continuous spectrum. That was wrong. Now, what has the name MGUS is actually monoclonal gammopathy of definite significance—MGUS is the earliest form of myeloma. Plasma cells of MGUS even show the same chromosomal translocation as in myeloma. Patients are **asymptomatic**. There is about a 1% chance of MGUS becoming myeloma every year. MGUS develops in the same demographic as myeloma—those over 60. Depending on age and functionality, the patient may die before they transform. Treatment is not given for MGUS, but regular surveillance for transformation is maintained.

Smoldering myeloma is what you call the disease between MGUS and multiple myeloma. Patients are asymptomatic but have an M spike like in MGUS. Patients have a hypercellular marrow with > 10% plasma cells like myeloma. But there aren't Bence Jones proteins, lytic lesions, or any symptoms. Seventy-five percent of patients with MGUS progress to multiple myeloma over a 15-year period.

Multiple myeloma is the real disease, with symptoms of Old CRAB, hypercellular marrow, etc.



(a) (b)

Figure 5.4: Multiple Myeloma Plasma Cells
(a) Plasma cells in bone marrow. (b) Plasma cells in blood smear.

Plasma cell leukemia is end-stage multiple myeloma. Plasma cells acquire multiple translocation mutations, as mentioned above, including expression of BCL-2, c-Myc, and cyclin D. The plasma cell lymphoma, which was limited to the bone marrow, becomes plasma cell leukemia. If you are presented a bone marrow biopsy with plasma cells, it is multiple myeloma. If given a **blood smear with plasma cells**, it is plasma cell leukemia.

Plasmacytomas are solitary lesions. Every lytic lesion in multiple myeloma is a single plasmacytoma. There are cases where there is a **solitary plasmacytoma**. In this case, resection of that singular plasmacytoma alleviates the disease.

Lymphoplasmacytic Lymphoma

This cancer causes a hyperviscosity syndrome known as **Waldenstrom's macroglobulinemia**. The proper name for the lymphoma is **lymphoplasmacytic lymphoma** (LPL). You should see it not as a lymphoproliferative disorder (not a B-cell leukemia or a B-cell lymphoma) but as the **other immunoglobulin-secreting cancer** next to multiple myeloma. LPL secretes IgM. When IgM causes symptoms of hyperviscosity, it is called Waldenstrom's. You should associate LPL as a synonym for Waldenstrom's, as either will be used to describe the same cancer on the exam.

LPL is a cancer of lymphoid origin that **differentiates into plasma cells**. Unlike myeloma, these plasma cells have not undergone somatic hypermutation or isotype switching. Therefore, they only express **IgM**. IgM forms pentamers, meaning the circulating dysfunctional antibody it secretes is enormous compared to IgG or IgA. IgG and IgA couldn't get out of the plasma in multiple myeloma. IgM most certainly will not be able to get out of plasma. LPL does not secrete any light chains. Which means there isn't any renal failure or amyloidosis. LPL doesn't induce osteoclasts to clear bone. So why learn LPL next to MM?

Because LPL presents with an **M spike**. This time, the M spike happens also to be IgM. If you have the information of "there is an M spike," it could be any of the myeloma spectrum or it could be LPL. LPL presents with symptoms created by a lot of very large IgM stuck in the plasma, increasing the viscosity of blood, presenting with **hyperviscosity syndrome** characterized by the following:

Visual impairment associated with venous congestion and retinal hemorrhages

Bleeding because IgM pentamers complex with clotting factors and platelets

Cold agglutinin disease (caused by IgM or *Mycoplasma*) presenting with Raynaud's and hemolysis

Neurologic problems of any kind, usually headaches, stupor, or vertigo, stemming from sluggish blood flow out of the brain's veins

Because all of the symptoms are caused by circulating IgM antibodies causing hyperviscosity syndrome, removing those antibodies with **plasmapheresis** reduces viscosity and alleviates symptoms. It is a difficult cancer to treat, and the median survival is 4 years.